Environmental Defense Comments on Cyclohexanol

(Submitted via Internet 3/21/02)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for cyclohexanol.

Cyclohexanol is used in the production of intermediates for nylon, plasticizers and selected agricultural chemicals. The sponsor claims that environmental releases are limited to air emissions at manufacturing sites although no data are provided to substantiate this claim. Although data on environmental releases and human exposure are not explicitly required under the HPV program, they are helpful in understanding the life cycle of a particular chemical or group of chemicals. Human exposure occurs primarily in the workplace and exposures appear to be less than 5ppm. Workers should be required to take protective measures to prevent skin contact, as dermal absorption of cyclohexanol is known to readily occur.

Cyclohexanol appears to be biodegradable in oxygen containing environments. However, the sponsor proposes to conduct a study to determine hydrolysis rates in water. We agree with this proposal. Adequate data are available on ecotoxicity of cyclohexanol including data for fish so no further ecotoxicity studies are needed. Cyclohexanol possesses low acute toxicity in rodents via several routes of administration and we agree that no acute toxicity studies should be performed. Cyclohexanol is negative in in vitro and in vivo tests for genotoxicity and no additional genotoxicity tests are needed to fulfill requirements under the HPV program.

There is data available in the scientific literature from repeat dose studies that indicates a wide spectrum of effects including effects on the central nervous system, liver and kidney. The sponsor considers these studies to be inadequate because they were not conducted under GLP. Therefore, a 90-day repeat dose inhalation study is proposed. The study design for the proposed study is critical. We urge the sponsor to use doses that span those used in the published studies where adverse effects were observed. Adverse effects have also been observed when cyclohexanol is administered via the dermal route. Data from the proposed inhalation study should not be used to discount the results from publications using the dermal route unless valid physiologically-based pharmacokinetic models are developed that accurately predict the delivery of cyclohexanol and its key metabolites to target tissues.

The sponsor intends to use results from the proposed inhalation repeat dose study to determine the nature of reproductive/developmental studies to be performed later. If histological data are positive for adverse effects on the gonads then a one-generation inhalation reproductive study will be conducted in rats to assess functional effects on fertility and reproductive performance. We recommend that the one generation reproductive study be conducted regardless of the outcome of the repeat dose study because there is data in the published scientific literature indicative of adverse effects in the male reproductive tract. Accordingly, initiation of the one-generation study should not be delayed pending completion of the repeat dose study.

Thank you for this opportunity to comment.

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